April 18, 2002

American Chemistry Council
Attn: Patricia A. Messenger
1300 Wilson Boulevard
Arlington, VA 22209

Dear Ms. Messenger:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for Low 1,3-Butadiene C4 Category, posted on the ChemRTK HPV Challenge Web Site on September 27, 2001. I commend the American Chemistry Council Olefins Panel for its commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its HPV Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the attached Comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that the American Chemistry Council Olefins Panel advise the Agency, within 90 days of the posting on the Web site, of any modifications to its submission.

If you have any questions about this response, please contact Richard Hefter, Chief of the HPV Chemicals Branch, at 202-564-7649. Submit questions about the HPV Challenge Program through the HPV Challenge Program Web site "Submit Technical Questions" button or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

/s/

Oscar Hernandez, Director
Risk Assessment Division

Attachment

cc: W. Sanders
A. Abramson
C. Auer
M. E. Weber

EPA Comments on Chemical RTK HPV Challenge Submission:
Low 1,3-Butadiene C4 Category

SUMMARY OF EPA COMMENTS

The sponsor, the American Chemistry Council Olefins Panel, submitted a test plan and robust summaries to EPA for the "Low 1,3-butadiene C4 Category" dated July 13, 2001. EPA posted the submission on the ChemRTK HPV Challenge Web site on September 27, 2001. The low 1,3-butadiene C4 category contains seven process streams arising from the ethylene manufacturing process, associated butadiene purification process, and other related C4 processes. Four of these process streams are complex mixtures and the remaining three describe higher-purity hydrocarbons.

EPA has reviewed this submission and has reached the following conclusions:

1. Category Justification. The category appears appropriate to include products of the ethylene process and associated C4 processes. However, the submitter needs to clarify how the CAS numbers listed in the test plan relate to the category process streams and whether the descriptions of process streams or CAS numbers define the members of the category. In addition, the submitter needs to provide a description of the ambiguously named C4 raffinate 1 component "carbonyl."

2. Physicochemical and Environmental Fate Data. The submitter needs to provide measured data to fill some of the physicochemical data gaps. For estimating the transport and distribution of these chemicals, EPA recommends using the EQC Level III model (see specific comments under Test Plan).

3. Health Effects. The submitter's proposal to characterize the health effects of the seven processing streams in this category by examining the toxicity of the major components of each stream and some related mixtures appears reasonable. EPA agrees with the use of data from other proposed testing under the HPV Challenge or OECD SIDS programs (sponsored through Petroleum HPV Testing Group and ICCA) to address the health effects endpoints assuming that the proposed testing is performed. The proposed repeated-dose/reproductive/developmental effects/neurotoxicity screen on 1-butene also will meet these endpoints. EPA recommends an appropriate OECD Guideline and GLP compliant testing for evaluation of the acute inhalation toxicity and mutagenic potential of 1-butene.

4. Ecological Effects. The submitter plans to conduct no ecotoxicity testing, but will provide the results of ECOSAR model runs. This is acceptable as long as the submitter also provides robust summaries on analog compounds so that the ECOSAR results can be verified for this class of compounds. In addition, the Structure-Activity Relationships (SAR) and any analog data need to be submitted in robust summary format. See EPA's guidance on the use of SAR and developing the Robust Summaries in EPA's HPV Challenge Program Guidance at the following website:
http://www.epa.gov/oppt/chemrtk/guidocs.htm.

EPA requests that the Submitter advise the Agency within 90 days of any modifications to its submission.

EPA COMMENTS ON THE LOW 1,3-BUTADIENE C4 CATEGORY CHALLENGE SUBMISSION

Category Definition

The low 1,3-butadiene C4 category contains seven ethylene process streams that originate from either a butadiene extraction process unit (C4 raffinate 1 stream) or the C4 cut of a catalytic cracker (catalytic butylenes stream). In addition to these two streams, the category contains C4 raffinates 2 and 3, isobutylene, 1-butene, and butane, all of which are obtained from C4 raffinate 1. Four of these process streams, catalytic butylenes and C4 raffinates 1, 2, and 3, are complex mixtures and contain varying percentages of propane, propylene, propadiene, n–butane, isobutane, isobutylene, 1-butene, *cis/trans* isomers of 2-butene, 1,3-butadiene, and other butenes. The other three process streams consist of the purified compounds, *n*-butane (**.** 88%), isobutylene (**.** 99%), and 1-butene (**.** 99%). The submitter identified eight CAS numbers that apply to the mixtures and purified compounds in this category.

The submitter states that, other than *n*-butane (CAS# 106-97-8), isobutylene (CAS# 115-11-7), and 1-butene (CAS# 106-98-9), it is difficult to assign a single specific CAS number to each of the four process streams; one CAS number may represent more than one process stream, and other multiple CAS numbers may represent one process stream. The submitter does not state, however, how accurately the CAS numbers collectively represent the members of this category (e.g., whether the CAS numbers can be used to describe process streams other than the ones in this category). The submitter also does not state whether the text descriptions of the process streams or the CAS numbers define the members of the category. For example, none of the process streams contain methane or ethane according to Table 2 of the test plan, but CAS number 68527-19-5 contains both. Therefore, the submitter needs to specifically state which definition predominates and how the CAS numbers listed in the test plan relate to the category process streams.

Finally, a number of components of the process streams are not adequately discussed or described. Table 2 of the test plan lists both acetonitrile and "carbonyl" as components of C4 raffinate 1, but neither component is discussed in the test plan. This is especially important for "carbonyl" because the name is ambiguous. In addition, the submitter notes that "cracked gas may also contain relatively small concentrations of organic sulfur compounds," but no discussion is presented in the test plan that describes what compounds are present and at what typical concentrations.

Category Justification

No single clearly stated rationale for grouping the process streams and single components in this category was presented in the test plan. It is apparent, however, that the members of the category are contained in sequential or related petroleum process streams (i.e., those hydrocarbons that remain in the crude butadiene stream after removing 1,3-butadiene as well as the C4 components from a catalytic cracker) and are related structurally. In addition, the physical and chemical properties of the stream components will closely follow their structure (while the chemical properties of the alkenes will be significantly different from the alkanes, reactivity for each type will follow structure). The grouping of these streams/chemicals is therefore supportable.

The submitter's approach to use toxicology data on the individual components of the process streams and data on some mixtures to define the toxicity of mixtures in this category appears acceptable.

Test Plan

Chemistry (melting point, boiling point, vapor pressure, water solubility, and partition coefficient)

The submitter needs to provide measured data for vapor pressure and water solubility for the three purified compounds, *n*-butane, isobutylene, and 1-butene, in this category.

Environmental Fate (photodegradation, stability in water, biodegradation, transport/distribution)

Biodegradation
The submitter's approach to biodegradation is adequate for the purposes of the HPV Challenge Program.

Transport and Distribution
For estimating transport and distribution (fugacity), EPA recommends using the EQC Level III model, which is more realistic and useful than the level I model for estimating a chemical's fate in the environment. In order to develop the Level III Fugacity model, EPA recommends using the EQC Level III model from the Canadian Environment Modeling Centre at Trent University, which allows full control of data inputs. This model can be found at the following web address: http://www.trentu.ca/academic/aminss/envmodel.

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive and developmental toxicity)

The test plan proposes to characterize the health effects of the seven process streams in this category by examining the toxicity of their major components and some related mixtures. This will be accomplished by compiling and assessing the results of tests performed under different test plans (sponsored through ICCA, the Petroleum HPV Testing Group and/or the SIDS program). The submitter has coordinated the testing under these programs so that the results of the tests will be broadly applicable to a number of petroleum process streams. The submitter anticipates that, in the aggregate, the test data collected from these programs will accurately reflect the toxicity of the low 1,3-butadiene C4 category members. The studies referenced in the test plan address testing for *n*-butane, isobutane, isobutylene, 1-butene, and 2-butene and for 1,3-butadiene-containing process streams. The low 1,3-butadiene C4 category test plan is focused on testing 1-butene.

While the overall design of the test plan was acceptable, the plan did not discuss all aspects of characterizing the low 1,3-butadiene C4 category. Specifically, the test plan did not address acetonitrile or "carbonyl," which were present at concentrations of up to 50 ppm in the C4 raffinate 1 stream (see Table 2 of the test plan). The submitter needs to provide a discussion on the potential contribution of these compounds to the toxicity of this stream since testing is not proposed. In addition, the test plan did not explicitly address the isomeric composition or testing of the butanes or butenes, which are major components (40-60%) of the catalytic butylenes process stream. Table 3 of the Test Plan indicates that the toxicity of the catalytic butylenes streams will be determined by the read-across method. This strategy is valid so long as the individual butanes and butenes have similar toxicities.

Comments on the adequacy of data for specific endpoints are provided below.

Of the 20 health effects robust summaries included with the test plan, the submitter used only the four robust summaries on 1-butene as a primary source of toxicity information to form the basis of the testing adequacy assessment for the chemicals in this category. Although 16 robust summaries were provided for 2-butene and isobutylene, the adequacy of testing for these chemicals is based on data either discussed in or generated from testing performed under the OECD SIDS and other HPV Challenge testing programs, respectively. The submitter needs to provide the rationale for not including robust summaries referenced for *n*-butane, isobutane, and crude butadienes. The ultimate acceptability of this test plan therefore depends on the acceptability of the other referenced test plans (i.e., the testing needs of *n*-butane and isobutane will be evaluated in the future by the Petroleum HPV Test Group, isobutylene and 2-butene are being sponsored under the OECD SIDS program, and crude butadiene (mixed C4s) will be tested as part of the Crude 1,3-Butadiene C4 Category).

Acute Toxicity. Except for a rat study on 2-butene, robust summaries submitted for the acute toxicity endpoint were based on research studies on the anesthetic properties of unsaturated gases following a 20-

minute exposure. The protocols used in the study did not conform to standard methods for determination of acute toxicity, and LC_{50} values were not calculated. EPA does not agree with the submitter's assessment that no additional acute toxicity testing for 1-butene is needed. EPA recommends that the submitter conduct an OECD-compliant study to characterize the acute toxicity of 1-butene.

Repeated Dose Toxicity. EPA agrees with the submitter's proposal to perform a combined repeated- dose/ reproductive and developmental effects/neurotoxicity screen (OECD TG 422) in rats via inhalation, on high purity 1-butene. EPA considers the existing repeated-dose oral toxicity study on isobutylene inadequate for characterizing the endpoint because the high volatility of the compound prevented accurate dosing of the test animals.

Genetic Toxicity. The submitter has not planned to conduct additional testing for this endpoint. However, EPA considers data submitted on 1-butene and a mixture of 1-butene and 2-butene inadequate to characterize the mutagenic potential of these compounds. The deficiencies noted in these studies included poor documentation, limited replication, and lack of measured concentrations for the test gases. The bacterial mutagenicity study was a method developmental study and was not adequately validated. EPA recommends that the submitter conduct an OECD-compliant study on 1-butene.

Reproductive and Developmental Toxicity. No robust summaries for reproductive or developmental studies were submitted for 1-butene. EPA agrees with the submitter's proposal to perform a combined repeated-dose/reproductive and developmental effects/neurotoxicity screen (OECD TG 422) in rats via inhalation on high purity 1-butene.

Ecological Effects

The submitter indicated that aquatic toxicity testing was not appropriate for gaseous substances like those in the category. Therefore, the submitter plans to provide calculated data from ECOSAR to satisfy the ecotoxicity endpoint requirements.

Despite relatively high volatility (based on high vapor pressures and Henry's Law constants), the category substances may still enter the aquatic ecosystem and have sufficient lifetimes in water to have effects. The use of SAR for this category seems applicable; however, the submitter needs to specify the compounds for which calculations will be performed and justify the use of these as representatives for the range of structures found in the category. In order to verify that the ECOSAR predictions reflect the true toxicity of the category members, the submitter also needs to provide some corroborating test data from appropriate analogs. Due to the high volatility of these chemicals, it is important to verify that these tests were conducted in closed systems. If tests were conducted in open systems, negative results could reflect the choice of test system rather than the true toxicity of the substance. For more information on how to test difficult-to-test substances, refer to the OECD Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures (http://www.oecd.org/ehs/test/monos.htm).

Specific Comments on the Robust Summaries

Health Effects

Acute toxicity
Except for a rat study on 2-butene, robust summaries submitted for the acute toxicity endpoint were based on a research study on the anesthetic properties of unsaturated gases. The protocols used in the study did not conform to standard methods for determination of acute toxicity, and LC_{50} values were not calculated.

Genetic toxicity

Although the robust summaries for the two *in vivo* micronucleus assays on 1-butene or isobutylene and a chromosome aberration study on 2-butene lack some information, they are considered adequate for the purposes of the HPV Challenge Program. The following information would enhance these summaries: (1) for the summary of 2-butene, the method used to process cells for analysis, the method of scoring aberrations and the frequency data for aberrations by type; (2) for the micronucleus assay on 1-butene, the source of bone marrow and method of slide preparation, criteria for scoring micronuclei, the mean standard deviation for the frequency of micronuclei in immature erythrocytes for each group, and the purity of the1-butene used in the test; (3) for the micronucleus induction assay of isobutylene, a rationale for dose selection, criteria for scoring micronuclei, and the mean standard deviation for the frequency of micronuclei in immature erythrocytes in each test and control group.

Repeated-dose toxicity

The summaries would be enhanced by including the following information: for the summary for the 2-butene study, numerical data for apparent treatment-related responses and for the isobutylene study, information on test conditions, measured concentrations in the test chamber, and the identity of tissues preserved and examined for histopathology.

Reproductive toxicity

Although the robust summary for 2-butene lacks some information, the study is adequate to characterize the endpoint. The summary would be enhanced by including the following information: numerical data on post-implantation loss, including historical control values; total live births; a table presenting the number of pups in each litter, weights of each litter, and mean pup weights; and data for food consumption and body weight.

Followup Activity

EPA requests that the Submitter advise the Agency within 90 days of any modifications to its submission.